APPENDIX I

PDR®
50
EDITION
1996

PHYSICIANS' DESK REFERENCE®

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ISBNs: 1-56363-152-0 and 1-56363-156-3

the legs (as measured by the I-125 ...ography) and of clinical pulmo... widely used dosage is 5,000 units ...ery and 5,000 units given every 8 to ...days or until the patient is fully ...is longer. The heparin is given by ...fat, ie, above the iliac crest or ab... thigh) injection with a fine (25- to ...imize tissue trauma. A concentrated ...ium is recommended. Such prophy... for patients over the age of 40 who ...surgery. Patients with bleeding disor... brain or spinal-cord surgery, spinal ...for potentially sanguineous opera... from this treatment, as should pa... anticoagulants or platelet-active drugs ...ue of such prophylaxis in hip surgery ...ed. The possibility of increased bleed... postoperatively should be borne in ...occurs; discontinuance of heparin and ...amine sulfate are advisable. If clini... embolism develops despite low-dose ...peutic doses of anticoagulants should ...indicated. Prior to initiating heparini... should rule out the probability of bleed... a thorough history and performing ...atory tests. Appropriate coagulation ...ed just prior to surgery. Coagulation ...normal or only slightly elevated at ...

Follow equipment manufacturers' ...carefully.

...addition of 400 to 600 USP units to ...blood for transfusion is usually em... ...ination. Usually, 7,500 USP units of ...mixed with 100 mL of 0.9% Sodium ...USP (or 75,000 USP units/1,000 mL of ...injection, USP); 6 to 8 mL of this ster... ...ed to each 100 mL of whole blood used. ...70 to 150 units of heparin sodium are ...10 to 20-mL sample of whole blood to pre... ...sample. Leukocyte counts should be ...ated blood within 2 hours after the ...rin. Heparinized blood should not be ...complement, or erythrocyte fragility ...platelet counts.

...ation (Heparin Lock) Sets—To pre... ...heparin lock set following its proper ...arin solution (see USP monograph for ...solution, USP) should be injected via ...quantity sufficient to fill the entire set ...solution should be replaced each time ...used. Aspirate before administering any ...in order to confirm the patency and lo... ...catheter tip. If the drug to be adminis... ...with heparin, the entire heparin lock ...ed with sterile water or normal saline ...medication is administered; following ...flush, the dilute heparin solution may ...be. The set manufacturer's instructions ...specifics concerning the heparin lock ...ven time.

...injections of small doses of heparin ...activated partial thromboplastin time ...value for APTT should be obtained prior ...arin lock set.

...

...units/mL, 5 mL (No. 520)—(1s) NDC ...

...store at controlled room temperature, 59° ...

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...origin) for Injection)

...

...ropin, rDNA Origin, for Injection) is a ...recombinant DNA origin. Huma... ...acid residues and a molecular weight of ...the amino acid sequence of the product ...human growth hormone of pituitary ...synthesized in a strain of *Escherichia* ...ified by the addition of the gene for ...

...white, lyophilized powder intended ...intramuscular administration after ...of Humatrope contains 5 mg somat... ...IU or 225 nanomoles); 25 mg manni... ...1.13 mg dibasic sodium phosphate. ...sodium hydroxide may have been ...at the time of manufacture to adjust the pH. This product is oxygen sensitive. Each vial is supplied in a combination package with an accompanying 5-mL vial of diluting solution. The diluent contains water for injection with 0.3% *m*-cresol as a preservative and 1.7% glycerin added at the time of manufacture.

Humatrope is a highly purified preparation. The 1.7% glycerin content makes the reconstituted product nearly isotonic at a concentration of 2 mg of Humatrope/mL diluent. Reconstituted solutions have a pH of approximately 7.5.

CLINICAL PHARMACOLOGY

Linear Growth—Humatrope® (Somatropin, rDNA Origin, for Injection) stimulates linear growth in children who lack adequate normal endogenous growth hormone. In vitro, preclinical, and clinical testing have demonstrated that Humatrope is therapeutically equivalent to human growth hormone of pituitary origin and achieves equivalent pharmacokinetic profiles in normal adults. Treatment of growth-hormone-deficient children with Humatrope produces increased growth rate and IGF-1 (Insulin-like Growth Factor/Somatomedin-C) concentrations similar to those seen after therapy with human growth hormone of pituitary origin.

In addition, the following actions have been demonstrated for Humatrope and/or human growth hormone of pituitary origin.

A. Tissue Growth—1. Skeletal Growth: Humatrope stimulates skeletal growth in patients with growth hormone deficiency. The measurable increase in body length after administration of either Humatrope or human growth hormone of pituitary origin results from an effect on the growth plates of long bones. Concentrations of IGF-1, which may play a role in skeletal growth, are low in the serum of growth-hormone-deficient children but increase during treatment with Humatrope. Elevations in mean serum alkaline phosphatase concentrations are also seen. 2. Cell Growth: It has been shown that there are fewer skeletal muscle cells in short-statured children who lack endogenous growth hormone as compared with normal children. Treatment with human growth hormone of pituitary origin results in an increase in both the number and size of muscle cells.

B. Protein Metabolism—Linear growth is facilitated in part by increased cellular protein synthesis. Nitrogen retention, as demonstrated by decreased urinary nitrogen excretion and serum urea nitrogen, follows the initiation of therapy with human growth hormone of pituitary origin. Treatment with Humatrope results in a similar decrease in serum urea nitrogen.

C. Carbohydrate Metabolism—Children with hypopituitarism sometimes experience fasting hypoglycemia that is improved by treatment with Humatrope. Large doses of human growth hormone may impair glucose tolerance.

D. Lipid Metabolism—In growth-hormone-deficient patients, administration of human growth hormone of pituitary origin has resulted in lipid mobilization, reduction in body fat stores, and increased plasma fatty acids.

E. Mineral Metabolism—Retention of sodium, potassium, and phosphorus is induced by human growth hormone of pituitary origin. Serum concentrations of inorganic phosphate increased in patients with growth hormone deficiency after therapy with Humatrope or human growth hormone of pituitary origin. Serum calcium is not significantly altered in patients treated with either human growth hormone of pituitary origin or Humatrope.

INDICATION AND USAGE

Humatrope® (Somatropin, rDNA Origin, for Injection) is indicated only for the long-term treatment of children who have growth failure due to an inadequate secretion of normal endogenous growth hormone.

CONTRAINDICATIONS

Humatrope® (Somatropin, rDNA Origin, for Injection) should not be used in subjects with closed epiphyses.

Humatrope should not be used when there is any evidence of activity of a tumor. Intracranial lesions must be inactive and antitumor therapy complete prior to the institution of therapy. Humatrope should be discontinued if there is evidence of tumor growth.

Humatrope should not be reconstituted with the supplied Diluent for Humatrope by patients with a known sensitivity to either *m*-cresol or glycerin.

WARNING

If sensitivity to the diluent should occur, the vials may be reconstituted with Sterile Water for Injection, USP. When Humatrope® (Somatropin, rDNA Origin, for Injection) is reconstituted in this manner, (1) use only 1 reconstituted dose per vial, (2) refrigerate the solution (36° to 46°F [2° to 8°C]) if it is not used immediately after reconstitution, (3) use the reconstituted dose within 24 hours, and (4) discard the unused portion.

PRECAUTIONS

Therapy with Humatrope® (Somatropin, rDNA Origin, for Injection) should be directed by physicians who are experienced in the diagnosis and management of patients with growth hormone deficiency.

Patients with growth hormone deficiency secondary to an intracranial lesion should be examined frequently for progression or recurrence of the underlying disease process.

Because human growth hormone may induce a state of insulin resistance, patients should be observed for evidence of glucose intolerance.

Excessive glucocorticoid therapy will inhibit the growth promoting effect of human growth hormone. Patients with coexisting ACTH deficiency should have their glucocorticoid replacement dose carefully adjusted to avoid an inhibitory effect on growth.

Hypothyroidism may develop during treatment with human growth hormone, and inadequate treatment of hypothyroidism may prevent optimal response to human growth hormone. Therefore, patients should have periodic thyroid function tests and be treated with thyroid hormone when indicated.

Patients with endocrine disorders, including growth hormone deficiency, may develop slipped capital epiphyses more frequently. Any child with the onset of a limp during growth hormone therapy should be evaluated.

Intracranial hypertension (IH) with papilledema, visual changes, headache, nausea and/or vomiting has been reported in a small number of patients treated with growth hormone products. Symptoms usually occurred within the first eight (8) weeks of the initiation of growth hormone therapy. In all reported cases, IH-associated signs and symptoms resolved after termination of therapy or a reduction of the growth hormone dose. Funduscopic examination of patients is recommended at the initiation and periodically during the course of growth hormone therapy.

Carcinogenesis, Mutagenesis, Impairment of Fertility—Long-term animal studies for carcinogenicity and impairment of fertility with this human growth hormone (Humatrope) have not been performed. There has been no evidence to date of Humatrope-induced mutagenicity.

Pregnancy—Pregnancy Category C—Animal reproduction studies have not been conducted with Humatrope. It is not known whether Humatrope can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Humatrope should be given to a pregnant woman only if clearly needed.

Nursing Mothers—There have been no studies conducted with Humatrope in nursing mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Humatrope is administered to a nursing woman.

ADVERSE REACTIONS

Approximately 2% of 481 naive and previously treated clinical trial patients treated with Humatrope® (Somatropin, rDNA Origin, for Injection, Lilly) have developed antibodies to growth hormone, as demonstrated by a binding capacity determination threshold ≥ 0.02 μg/mL. Nevertheless, even these patients experienced increases in linear growth and other salutary effects of Humatrope and did not experience any unusual adverse events. Although growth-limiting antibodies have been observed with other growth hormone preparations (including products of pituitary origin), antibodies in patients treated with Humatrope have not limited growth. The long-term implications of antibody development are uncertain at this time.

Of the 232 naive and previously treated clinical trial patients receiving Humatrope for 6 months or more, 4.7% had serum binding of radiolabeled growth hormone in excess of twice the binding observed in control sera when the serum samples were assayed at a tenfold dilution. Among these patients were 160 naive patients, of whom 6.9% had positive serum binding. In comparison, 74.5% of 106 naive patients treated for 6 months or more with somatrem (produced by Lilly) in a similar clinical trial had serum binding of radiolabeled growth hormone of at least twice the binding observed in control sera.

In addition to an evaluation of compliance with the treatment program and of thyroid status, testing for antibodies to human growth hormone should be carried out in any patient who fails to respond to therapy.

In clinical studies in which high doses of Humatrope were administered to healthy adult volunteers, the following events occurred infrequently: headache, localized muscle pain, weakness, mild hyperglycemia, and glucosuria. In studies with growth-hormone-deficient children, injection site pain was reported infrequently. A mild and transient edema, which appeared in 2.5% of patients, was observed early during the course of treatment.

Leukemia has been reported in a small number of children who have been treated with growth hormone, including

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* Identi-Code® symbol. This product information was prepared in June 1995. Current information on these and other products of Eli Lilly and Company may be obtained by direct inquiry to Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, Indiana 46285, 800-545-5979.